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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/685,288	10/13/2003	George N. Cox III	4152-1-PUS-8	1441
22442	7590	10/24/2006	EXAMINER	
SHERIDAN ROSS PC 1560 BROADWAY SUITE 1200 DENVER, CO 80202			STOICA, ELLY GERALD	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/685,288

Applicant(s)

COX, GEORGE N.

Examiner

Elly-Gerald Stoica

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-70 is/are pending in the application.
- 4a) Of the above claim(s) 1-43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44-70 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>08/22/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

Detailed Action

Election/Restriction

1. Applicant's provisional election without traverse of Group III, claims 44-60, directed to a method of protecting an animal from a disease by treatment with a cysteine variant of Interferon- α 2 (IFN- α 2) in the reply filed on August 14, 2006, is acknowledged. Upon further consideration the Examiner has withdrawn the requirement for election of species within the restricted Group III.

Specification

2. The disclosure is objected to because of the following informality. The word "herein" is misspelled on page 15, line 32. The word "of" is misspelled on page 28, line 32. The address of the American Type Culture Collection found on page 57 of the specification is incorrect, as the ATCC has relocated. The present address is 10801 University Blvd., Manassas, VA 20110-2209. Amendment of the disclosure to correct the misspelled words and indicate the current address is required.

Priority

2. The instant application is a CIP of the non-provisional applications 10/400377 and 10/276358, as well as of US Pat. 6,608,183, US Pat. 6,753,165. The current application also claims benefit of the provisional applications 60/418,106 and 60/418,105. Since 10/685,288 is a continuation in part, the claims 44-51, 55, 56, 63-67

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and 69-70 will benefit from the 60/052516, 07/14/1997; claims 52-54 will benefit from 60/418,106 and 60/418,105 while claims 57-62 will be considered from the filling date of this instant application, 10/13/2003

Status of the claims

3. Currently, claims 44-70 are pending. Claims 1-43 were withdrawn pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44 and 45 as well as 46-70 (as dependent claims) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the IFN- α 2 Cysteine variants pertinent to these claims recited in WO 01/87925 (p24, lines 13-16), does not reasonably provide enablement for the other cysteine variants which are not part of the recitation and, correspondingly, located in the regions of the IFN- α 2 that contained the non-enabled construct. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

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the invention commensurate in scope with these claims. The specification is not enabling for the following IFN- α 2 cysteine variants: P4, Q20, S73, A74, A75 E78, T79, K112, E113, D114, S115, K131, E132, K133 K134 Y135, S136, A139, S152, S154, T155, N156, L157, Q158, E159, S160, L161, R162, S163, K164 and E165. Correspondingly, the specification is not enabling for substitution in the following regions of the IFN- α 2: the D-E loop, the first three or the last three amino acids in helix A, the first three or the last three amino acids in helix B, the first three or the last three amino acids in helix C, the first three or the last three amino acids in helix D, the first three amino acids in helix E.

The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to a genus of Interferon- α 2 variants described as having a cysteine residue substituting certain amino acid residues and having an in vivo ability to treat an animal for a disease treatable by IFN- α 2.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

- 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation

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needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In the present case, the Applicant has provided a structural limitation (substitution of an amino acid with a cysteine) and a functional limitation (the treatment of an animal in need for treatment with IFN- α 2). The cysteines are needed for PEGylation of the modified growth factor for increase of the half-life of the variants of the IFN- α 2 claimed. The state of the prior art is adequate for the conceptual construction of cysteine mutants or PEGylated growth factors (Cunningham and Wells, Science 244, 1081-1085, Goodson and Katre, Biotechnology 1990, 343-6). Even though the relative skill existent in the art at the time of the priority date claimed would permit the making of certain cysteine mutants for Growth Hormone (US Pat. 6,608,183), in the specification no data are presented as to representative mutants formed substitution of cysteine residues in all the substructures claimed. There are teachings in the art that underscore the uncertainty in protein modification in general and in the effects of modifying any particular residue in a protein sequence absent specific teachings relating the amino acid to the protein's function and structure (Bowie et al., Science 247, 1306-1310). In the specification, the Applicant proposes "rules" for the modification of the target proteins, members of the Growth Hormone super family, (pages 12 and 13 of the specification) with three key components.

First, the specification identifies as preferred sites for modification those regions of the Growth Hormone supergene family corresponding to the pre-Helix A region, and

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the region distal to the last helix of the protein, and the A-B, the B-C, the C-D loops (i.e. the loop regions) of the proteins (page 12, lines 10-32, page 13, lines 5-12)

Second, the application additionally indicates that N- and O- glycosylation sites may also be preferred sites for protein modification (page 13, lines 13-34). Finally, the application teaches that these rules may be applied to other proteins, and that in such other proteins the amino acids that can be replaced with cysteine without significant loss of "biological activity", as is the insertion of cysteine between two amino acids that are situated in the "disclosed" regions (p15, lines 11-15).

It is noted that, "where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus or combination claimed" In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973). Thus, where there is uncertainty in the art, even the presence of multiple species within a claimed genus does not necessarily demonstrate possession of the genus. In the present case, the state of the art has provided a good deal of evidence supporting a finding of uncertainty in the art. However, the application provides only the teachings of the indicated "rules" to support the present claims to the genus. The rules and disclosed species are not deemed sufficient to overcome the uncertainties in the art. Several teaches in the art demonstrate that:

-modification of certain amino acids found within the pre-alpha helix region of the protein results in loss of protein activity;

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-amino acid deletion is not predictive of the effects of substitution modifications to the same residues;

-insertion of cysteine has a greater likelihood of disrupting protein structure.

Thus, significant evidence of uncertainty has been presented. The embodiment described in the specification and claimed is rather a prophetic one based on predicted results rather than work actually conducted or results actually achieved.

The strongest contradiction between the teachings in the art and the applicant proposed "rules" are the teachings of Shaw (U.S. 5,166,322) and Zurawski et al (EMBO Journal 12: 5113-5119). The last reference demonstrates that many "unimportant residues" in the GH superfamily protein IL-2 were intolerant to cysteine modifications. It is noted that an alignment of the IL-2 reference in Figure 1 of Zurawski with the structural teachings of IL-2 found in Bazan et al., (Science 257: 410-13) indicates that the A, B, C, and D helices of the portion of IL-2 correspond, respectively, to the following residues of the Figure 1 sequence: A, R41 (only the C-terminal residue of this helix shown); B, K.68-187; C, N99-K1 12; and D, V130-5142 (all of D helix not shown). Taking into consideration the teachings of the Bazan reference, the Zurawski reference indicates that certain residues found in the A-B loop, the last three residues of each of the A and C helices, and in the first three residues of the C helix are found among those residues described as intolerant to cysteine substitutions. Thus, the reference supports the assertion that those in the art would not be able to predict, based on the teachings in the prior art, which amino residues would be tolerant to cysteine modification according to the teachings of Braxton (US patent 5,766,897). However, these same

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teachings also demonstrate that cysteine substitutions may not be made freely among the residues in various regions identified by the first "rule" presented in the application. In view of these teachings, it appears that the application of the Applicant's first rule would still result in uncertainty in the operability of any particular IFN- α 2 variant.

The second "rule" provided by the application is similarly contradicted by the teachings of the Shaw reference. This reference "found that the glycosylation site in IL-3 (asparagine 15) is not useful for creating cysteine mutants in IL-3 because the mutant protein is not biologically active." IL-3 is also among the proteins identified in the application as a member of the GH superfamily. Thus, the teachings of this reference also demonstrate uncertainty in operability of protein variants even upon the application of the second rule. Moreover, the art, and in particular Zurawski, indicate that the effect of the cysteine substations varies with amino acid being substituted. For example, residue 42 (in the A-B loop) of IL-2 was indicated to be intolerant to cysteine substitution, whereas the substitution of amino acids 43 and 44 had relatively little effect on the protein activity. In the case of IFN- α 2 Grosfeld et al. showed that the residues 10-21(A helix and A-B loop are critical for interaction with Interferon receptor and thus the cysteine mutants in this region will lose the biological effect. While the claims include both structural and functional requirements, the teachings of the Zurawski and of the Grosfeld reference indicate that the structural requirements fail to correlate with the functional requirements. In view of the lack of correlation between the structures and functions relied on to describe the claimed genus, and the evidence of uncertainty in the operability of any particular species of the claimed invention, even upon the application

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of the "rules", the teachings of the application are not deemed sufficient to provide descriptive support for the claimed genus of IFN- α 2 variants, without undue experimentation needed to obtain the particular bio-active IFN- α 2 mutants.

Claim 44 of the instant application also contains the term "protect an animal from a disease" which, as defined in specification, refers to "reducing the symptoms of a disease, reducing the occurrence of the disease, and /or reducing the severity of the disease" (p.23 lines 25-27 of the specification). However, at line 30-31 of the specification, the Applicant uses the term "prophylactic treatment" for the same "protect an animal from a disease". It is noted that, at time of the Invention, studies from different groups on prophylaxis in animal were numerous but "prevention of infection has been observed sporadically" and not achieved consistently and in a reproducible manner (Black, RJ, Am. J. Med. **102**, p 40. left column, last paragraph). It appears that, by limiting to the original definition offered, the claim is better defined.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The Applicant is encouraged to provide any evidence that the disclosure enables the claimed invention.

Claim 68 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a new matter rejection.

The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The mutant R23K in the claim has not been described at all in the specification and was added in the Applicant's response after the election/restriction office action.

The Applicant is encouraged to point to where in the specification support for the newly recited subject matter may be found.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 44, 52-62 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glue et al. (US pat. 6,177,074) in view of Katre et al. (US pat. 5,206,344).

The claimed invention is drawn to a method to protect an animal from a disease or condition that can be treated by alpha interferon, comprising administering to an animal a composition comprising a cysteine variant of alpha interferon that has at least one cysteine residue substituted for an amino acid from the disclosed regions of the

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alpha interferon. The cysteine mutant is modified with a cysteine reactive moiety which can be polyethylene glycol and used to treat cancer, viral diseases, Hepatitis B and Hepatitis C, leukemia, melanoma and Kaposi's sarcoma and inhibits viral growth and growth of tumor cells.

Glue et al teaches a method of treating viral infections, in particular, viral infections that are susceptible to treatment with interferon alpha, comprising the subcutaneous administration of an amount of a polyethylene glycol-interferon alpha conjugate, which amount is effective to treat the viral infection while reducing or eliminating adverse side effects normally associated with administration of interferon alpha. In a preferred embodiment of the invention, administration of a polyethylene glycol having an average molecular weight of 12,000 conjugated to interferon alpha is used to treat chronic hepatitis C (column 1, lines 15-26 and column 2, lines 20-21). Glue et al. also teaches that the objective of conjugation of IFN alpha with PEG is to improve the delivery of the protein by significantly prolonging its plasma half-life, and thereby provide protracted activity of IFN alpha (column 3, lines 66-67, column 4, lines 1-3). Regarding the conditions to be treated, Glue et al. teaches that conditions that can be treated with interferon include but are not limited to cell proliferation disorders, in particular cancer (e.g., hairy cell leukemia, Kaposi's sarcoma, chronic myelogenous leukemia, multiple myeloma, basal cell carcinoma and malignant melanoma, ovarian cancer, cutaneous T cell lymphoma), and viral infections. Glue et al. does not teach the use of PEGylated cysteine variants.

Katre et al. (column 3 line 34 to column 4 line 62) teach an IL-2 mutein conjugated to poly ethylene glycol (PEG) comprising a mutein that contains a cysteine non-essential for bioactivity coupled by a thio ether bond. Katre et al. teach that the cysteine muteins are beneficial for making PEG conjugates for increasing the physiological half-life of the protein and to decrease the immunogenicity of the protein in vivo.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made cysteine variants of the alpha interferon taught by Glue et al. as a convenient means of making PEG conjugates and reducing immunogenicity in order to obtain a longer half life of the alpha interferon. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success because Katre et al. teach that the PEGylation process is based on the physico-chemical properties of the non-essential reactive cysteine and not on the nature of the peptide used.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Jacob et al. (WO/2002/044717). Jacob et al. teaches that, for the peptides that are used to treat hepatitis C, the modes of administration in the animal model can be "parenteral, intravenous, intradermal, intra-articular, intra-synovial, intrathecal, intra-arterial, intracardiac, intramuscular, subcutaneous, intraorbital, intracapsular, intraspinal, intrasternal, topical, transdermal patch, via rectal, vaginal or urethral suppository, peritoneal, percutaneous, nasal spray, surgical implant, internal surgical paint, infusion pump, or via catheter. In one embodiment, the agent and carrier

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are administered in a slow release formulation such as an implant, bolus, microparticle, microsphere, nanoparticle or nanosphere. The preferred mode of administering is intravenous.

Conclusion


6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elly-Gerald Stoica whose telephone number is (571) 272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


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